REMARKS

The Office Action of April 1, 2003 presents the examination of claims 43, 45, 51, 52 and 63-70.

The present paper amends claims 43, 45, 51, 63, 64, 67 and 70. The amendments to the claims do not change their scope, but rather merely incorporate language of the specification that defines terms previously deemed unclear by the Examiner.

Claim 71 is newly presented. The recitation that the RNA is introduced into the cell by transfection is supported by the specification at, e.g. page 12, line 26.

Oath alleged defective

The Examiner alleges that the Oath or Declaration of the inventors filed in the original application is insufficient because the present application, via preliminary amendment of the parent application 09/371,510 on August 10, 1999, introduced subject matter not attested to as being claimed in the original application. The Examiner takes a position that the present application is therefore a Continuation-In-Part application of the original application 07/920,281 (through the intervening Continuation application of 08/466,277).

As a formal matter, Applicants will provide a supplemental Declaration of the inventors as the Examiner has requested at

such time as the claims are otherwise considered to be in condition for allowance. Applicants concede that the language of the present claims is different from that used in the original '277 application and are willing to provide reassurances that the instant claims relate to an invention made by the present inventors. However, Applicants do not concede that the presently claimed subject matter is not adequately disclosed in the original '277 application and, as explained below, assert entitlement to at least the filing date of the '277 application (the December 12, 1991 filing date of the PCT application) for the present claims.

Objection to the specification and Rejection under 35 U.S.C. § 102(e)

The Examiner objects to the specification as failing to provide antecedent basis for claims 43, 45, 51, 52 and 63-70. These claims are then rejected under 35 U.S.C. § 102(a) or § 102(e) as anticipated by Johnston et al. '462. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner institutes the instant rejection in view of his position that the present claims are only entitled to a filing date of August 10, 1999. Applicants submit to the contrary that the present specification, which but for addition

of Sequence Listing identifiers is identical to that filed as PCT/SE91/00855 on December 12, 1991, provides adequate written description support and enablement of the invention recited in claims 43, 45, 51, 52 and 63-70.

> The test for compliance with § 112 has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing. *See, Vas-Cath*, 935 F.2d at 1561 ("Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation").

Moba B.V. v. Diamond Automation, Inc., 66 U.S.P.Q.2d 1429, 1439 (Fed. Cir. 2003). The assessment is made from the viewpoint of one skilled in the art. *Id.* at 1439.

Applicants submit that one of ordinary skill in the art, reading the present specification, would conclude that the inventors possessed the invention of claims 43, 45, 51, 52 and 63-70 at the time of filing of the PCT/SE91/00855 application. Applicants' explanation in this regard relies upon page and line numbering of the instant application rather than that of the published PCT application, as the two are identical in their relevant text and drawings.

The features that the Examiner asserts are not disclosed in the US '277 application (or by implication the PCT '855 application) are:

1. helper cells;
2. alphavirus replicons;
3. limitations of more than one helper RNA;
4. characteristics of the helper RNAs; and
5. properties of the replicons.

Applicants explain the support for each of these concepts below.

1. Helper cells

The concept of a helper cell is explicitly described at page 10, lines 4-6. Here the reader finds "help" described as the provision of "trans complementation". This term is well-understood by the skilled artisan to mean that a biochemical function not provided by one entity is provided by some second entity. This disclosure should be read together with that at page 8, lines 15-18, which describes one embodiment as a recombinant alphavirus comprising an exogenous RNA that replaces "deleted structural protein region(s)" and with page 9, lines 11-24, which describes one embodiment of a "helper" system as one in which one RNA molecule is a recombinant RNA molecule as above and a "helper" RNA is one carrying replication signals and nucleic acid encoding "viral structural proteins", but lacking

non-structural proteins and packaging signals. Trans complementation effects formation of infectious virus particles when both nucleic acids are present in a single cell, as now all of the viral structural proteins are made within one cell and a particle can be assembled. This concept is also illustrated in Figures 7C and 9.

2. alphavirus replicons

Applicants concede that the term "alphavirus replicon" is not used in the specification. This term was created in the claims as a convenient substitute for the term "recombinant alphavirus vector". This latter term is now utilized and applicants believe it is well-understood from the specification. *See, e.g.*, page 15, line 25 ("SFV vector") and Figure 8 (showing one embodiment), and original claim 13.

3. More than one helper (nucleic acid)

Applicants submit that the person of ordinary skill in the art of viral vector development at the time the PCT '855 application was filed would understand that the concept of trans complementation and helper nucleic acids as exemplified in (1.) above extended to both use of DNA rather than RNA vectors and to use of multiple helper vectors to complement "defects" (e.g., deletions) of multiple structural proteins.

First, the present application describes use of DNA vectors useful either for *in vitro* transcription (page 9, lines 15-18) or for transformation of animal cells (page 12, lines 6-8). Thus, use of both DNA or RNA nucleic acids to implement the invention is well-described.

The specification also describes deletions of the complete or part of the region(s) encoding the virus structural genes. (See, page 11, lines 5-6.) This clearly indicates that more than one deletion in more than one gene was contemplated by the inventors at the writing of the specification.

The Examiner should further note that the specification discloses that there are four separate structural genes (Fig. 2), which can be isolated on restriction fragments as shown in Fig. 4. The disclosure at p. 9, lines 11-24 explains that the invention lies in a vector system in which the alphavirus recombinant genome includes from none to all but one of the structural protein genes and that complementation by helper vectors provides the missing structural protein genes. Applicants submit that this text and these figures suggest that any combination of vectors providing the complete complement of structural proteins is sufficient to practice the invention.

Furthermore, the Examiner should note originally-filed claim 20. Claim 20 defines a method for producing infectious alphavirus particles using "helper RNA transcribed in vitro from

a helper DNA." Helper RNA is not limited to a single species or RNA molecule and encompasses a plurality of helper RNAs each encoding a different structural protein.

The Examiner might also note original claims 12, 13 and 22. Claim 12 defines generally a DNA expression vector comprising a full-length or partial cDNA complementary to alphavirus RNA or parts thereof. Claim 13 describes the DNA vector as one having portions of the viral cDNA deleted, "the deletions comprising the complete or part of the region(s) encoding the virus structural proteins,…". Thus claim 13 includes a vector in which a deletion can occur within more than one structural gene.

Claim 22 defines a helper vector, e.g. for complementing the recombinant alphavirus vector of claim 13, which is comprised of the DNA vector of claim 12 in which the regions encoding virus non-structural proteins are almost completely deleted, but "the region encoding the promoter for the structural gene subgenome and those encoding the structural region are preserved." In the instance wherein the alphavirus vector of claim 13 includes deletions in multiple structural genes, clearly those multiple structural regions could be represented among a plurality of helper DNA vectors or helper RNA transcripts to obtain all of the structural proteins for complementation and claim 22 encompasses this embodiment.

Finally, original claim 25 recites a method for producing infectious alphavirus particles in which cells "transformed to produce helper RNA" are transfected with RNA transcript of a recombinant alphavirus vector. Again, "helper RNA" is not limited to a single transcript, but can be a plurality of different helper RNA molecules.

Applicants submit that the totality of the application, as described above, informs the reader of ordinary skill in the art that more than one helper vector, of either an RNA or DNA nature, was contemplated by the inventors at the time the application was filed.

4 and 5. characteristics of the helper (nucleic acids) and replicons

The Examiner states that the "characteristics of the helper RNAs" and "characteristics of the replicons" are not described in the specification. As explained in (3.) above, it is Applicants' position that the specification describes embodiments in which DNA as well as RNA vectors are utilized. Applicants take the "characteristics" of the helpers and replicons to be the particular arrangements of structural proteins carried by the helpers and replicons.

The presence of a packaging signal on the recombinant alphavirus vector, and lack thereof on a helper vector, is

described at page 8, line 32 and page 9, line 23, respectively and illustrated in Figure 9.

Figure 7C shows one particular arrangement in which all of the genes encoding alphavirus structural proteins are deleted from the "recombinant alphavirus vector" (or "replicon") and are present on a helper vector.

Claim 43 recites that at least one structural protein is encoded by the recombinant alphavirus vector, while at least one structural protein is not, and that the structural proteins not encoded by the recombinant alphavirus vector are encoded by at least one helper vector. Applicants submit that this arrangement is supported by the specification by the description of the general concept of trans complementation as explained in (1.) above and by the concept of use of one or more helper vectors as explained in (3.) above.

In one embodiment the E1 and E2 genes are on one helper. Figure 4 shows the E1 (as E1-6k precursor) and E2 (as E2-E3 polyprotein) as two adjacent transcripts, with appropriate restriction sites for separating them from the capsid protein gene. This figure suggests the arrangement of claim 43 to the skilled artisan. Claim 65 is also supported by this disclosure.

Claim 45 recites that at least one of the recombinant alphavirus vector and at least one helper vector includes a mutation in E1, E2 or E3. The E1, E2 and E3 proteins are the

spike structural proteins of the alphavirus as described at page 16, lines 29-34 and illustrated in Figure 1. At page 10, line 18, incorporation of a conditionally lethal mutation into the "structural part of the helper genome" is described. At page 11, lines 15-18, insertion of a "foreign epitopic peptide sequence", *i.e.* an insertional mutation, into a region encoding "viral structural proteins" is described.

Applicants submit that the above explanation establishes that the specification alone provides sufficient evidence that the inventors possessed the invention recited in claims 43, 45, 51, 52 and 63-70 at the time the PCT '855 application was filed. It is abundantly clear that the inventors are not overreaching; they have recounted their invention in such detail that [the present] claims can be determined to be encompassed within their original creation. Accordingly, the objection to the specification as failing to provide antecedent basis to the claims should be withdrawn and the present claims should be accorded the December 12, 1991 filing date of the PCT '855 application.

In view of the effective U.S. filing date of December 12, 1991, the Johnston '462 patent is not effective as prior art against the instant claims. Accordingly, the rejection of claims 43, 45, 51, 52 and 63-70 under 35 U.S.C. § 102(a) or § 102(e) should be withdrawn.

Applicants submit that the present application well describes and claims patentable subject matter. The favorable action of withdrawal of the standing rejections and allowance of the application is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), Applicants respectfully petition for a three (3) months extension of time for filing a response in connection with the present application. The required fee of $930.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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